CHALLENGES AND OPPORTUNITIES IN DESIGNING SMALL INTRAMURAL CLINICAL TRIALS

Mitchell Max, M.D.

OUTLINE

I. There are great opportunities for the well-prepared clinical researcher to advance the methods of therapeutic research.

Clinical trial methods were essentially invented in the late 1940's and 50's (Lilienfeld, 1982; Marks, 1988) to investigate therapeutic response in what were often thought to be rather homogeneous and well-understood clinical entities--typical questions were "Does pulmonary tuberculosis respond to streptomycin?" or "Does postoperative pain respond to morphine?"

In contrast, the major scientific question asked in most current NIH intramural clinical trials concern disease mechanisms, often in groups thought to be heterogeneous in this respect. Many studies combine probes of disease mechanisms with therapeutic trials (e.g. PET scans and neuropharmacology studies; oncogene studies and chemotherapy trials, etc.)

A few examples of current challenges in probing mechanisms in small patient subgroups will be briefly touched upon.

II. Explanatory vs Pragmatic Orientation in Clinical Trials: Implications for Study Design

Previous lectures discussed the choice of a scientific question. The way that a question about therapy of a disease is formulated will dramatically affect the choices one makes in designing a clinical trial. A crucial distinction in translating a clinical hypothesis into a specific study design was articulated by Schwartz and Lellouch (1967): In an "explanatory" approach, the main purpose of the study is to elucidate a biological principle about the treatment and disease, whereas a "pragmatic" approach seeks to guide the clinician's empirical choice of treatment for patients similar to those in the particular study.

I will use the example of a hypothetical clinical trial of various antidepressants in painful peripheral neuropathy to show how many of the design choices will differ in trials with "explanatory" versus "pragmatic" orientations.

"Explanatory" versus "pragmatic" orientations of clinical trials: effect on design choices in hypothetical painful neuropathy trial

	Orientation of clinical trial	
Design issue	**Explanatory**	**Pragmatic**
Main question	What neurotransmitter mediates analgesia?	What is the best tretment in clinical practice?

Patient choice	Selective A-beta mediated Definite neuropathy	Inclusive Probable neuropathy
Treatments	Pharm. specific Desipramine Fluoxetine	Clinical favorites, including combinations
Controls	Placebo	Other active medications
Dose	High; often fixed	Titrate as in clinic
Treatment conditions	Optimal	Corresponding to clinical practice
Analysis	Completers	Intent-to-treat

III. Issues in Phase 2 Single-Center Trials that Examine Both Disease Mechanism and Treatment Efficacy

A. Challenges

1. Disease mechanisms are often heterogeneous within a diagnostic category, and one doesn't yet know how to distinguish which mechanisms are active in which patients (Max, 1991)
2. Sample sizes are small, usually between 10 to 100.

B. Some approaches to these challenges:

1. Distinguish mechanisms

Clinical features--e.g. brief vs. steady pain

Physiological measures--biochemical, brain imaging

Genetic markers

2. Sledgehammer approach--design the study to maximize therapeutic effect. Maximize doses, screen out likely nonresponders.

3. Minimize experimental error

a. Pharmacokinetic approaches

Tailored drug infusions (Coda et al., 1993)

Concentration-controlled clinical trials (Peck, 1993)

b. Measurement strategies

Better tools (Rubinow lecture)

Design assessment with regard to time course of symptoms; e.g. assessments at multiple time points to lessen impact of fluctuations (Jensen & McFarland, 1993)

c. Crossover design

Conventional group studies (Louis et al., 1984; Jones and Kenward, 1989; Ratkowsky et al., 1993; Senn, 1993)

Enriched enrollment studies (Byas-Smith et al., 1995)

"N of 1" or single case designs (Guyatt et al., 1986)

IV. Placebo Responses in Clinical Trials

Placebo-sensitive vs. resistant outcomes in various diseases. The attached chapter by Howard Spiro points out that, not surprisingly, placebo responses have their most dramatic effects on symptoms, though some aspects of function (e.g. pulmonary function in asthma, blood pressure) may also be affected. There is little evidence for placebo effects on structural lesions.

Factors that influence placebo responses (e.g. expectations, nonverbal cues from clinicians , side effects of treatment), and implications for study design will be discussed, including the pros and cons of using "active placebos" with side effects that mimic the test drug (Moscucci et al., 1987; Greenberg and Fisher, 1994; Gaudet, 1985)

When are placebos needed? The eight cases in following illustration illustrate the logic of interpreting responses of subjective symptoms (e.g. pain, sedation, mood, nausea, fatigue, dizziness) to treatment in clinical trials. Note that a key question in any such studies is the reliability of measurement methods to pick up a favorable effect of a treatment. In studies of subjective effects, such failures of assay sensitivity are true negative result for a treatment. (See illustration on next page from Max and Laska, 1991.)

A current controversy about the use of placebos in clinical trials will be discussed (Taubes, 1995).

ATTACHED READINGS

Lilenfeld AM. Ceteris paribus: the evolution of the clinical trial. Bull. History Med 1982;56:1-18.

Marks HM. Notes from the underground: the social organization of therapeutic research. In: Maulitz RC, Long DE, eds. Grand Rounds: 100 Years of Internal Medicine. Philadelphia: University of Pennsylvania Press, 297-336.

Max MB, Laska EM. Single-dose comparisons. In: Max MB, Portenoy RK, Laska EM, eds. The Design of Analgesic Clinical Trials. New York: Raven Press, 1991: 73-75.

Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. J Chronic Dis 1967;20:637-648.

Spiro HM. Doctors, patients and placebos. New Haven: Yale University Press, 1986, pp. 75-96.

Taubes G. Use of placebo controls in clinical trials disputed. Science 1995; 267: 25-26.

OTHER REFERENCES IN OUTLINE

Byas-Smith MG, Max MB, Muir J, Kingman A. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two -stage enriched enrollment design. Pain 1995;60:267-274.

Coda B, Hill HF, Schaffer RL, Luger TJ, Jacobson RC, Chapman CR. Enhancement of morphine analgesia by fenfluramine in subjects receiving tailored opioid infusions. Pain 1993;52:85-91.

Gaudet RJ. Migraine prevention with beta blockers: a placebo effect? JAMA 1985; 254:3183-3184.

Greenberg RP, Fisher S. Seeing through the double-masked design: a commentary. Contr Clin Trials 1994; 15:244-246.

Guyatt GH, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy-- randomized trials in individual patients. New Engl J Med 1986;314:889-892.

Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain 1993;55:195-203.

Jones B, Kenward MG. Design and Analysis of Cross-Over Trials. New York: Chapman and Hall, 1989.

Max MB. Neuropathic pain. In: Max MB, Portenoy RK, Laska EM, eds. The Design of Analgesic Clinical Trials. Adv Pain Res Ther, vol 18. New York, Raven Press, 1991: 193-220.

Max MB, Laska EM. Single dose analgesic comparisons. In: Max MB, Portenoy RK, Laska EM, eds. The Design of Analgesic Clinical Trials. Adv Pain Res Ther, vol 18. New York, Raven Press, 1991:55-95.

Moscucci M, Byrne L, Weintraub M, Cox C. Blinding, unblinding, and the placebo effect: an analysis of patients' guesses of treatment assignment in a double-blind trial.

Peck CC. Concentration -controlled versus concentration-defined clinical trials. Clin Pharmacol ther 1993;53:385-387.

Ratkowsky DA, Evans MA, Alldredge JR. Cross-Over Experiments: Design, Analysis, and Application. New York: Marcel Dekker, 1993.

Senn S. Cross-Over Trials in Clinical Research. Chichester: John Wiley, 1993.

Challenges and Opportunities in Designing Small Intramural Clinical Trials

Mitchell Max, M.D.

Module I, Unit 3

1. Intent-to-treat analysis is more meaningful in:

   a. an "explanatory" clinical trial
   b. a "pragmatic" clinical trial
   c. equally meaningful in a. or b.

2. A one-month, parallel group clinical trial of treatments for chronic fatigue syndrome compared two treatments: an antiviral compound and an anitdepressant drug. Both lowered subjective ratings of fatigue on a standard scale for fatigue by 25%. One can conclude that:
   a. Both are effective treatments for chronic fatigue.
   b. Neither is an effective treatment for chronic fatigue.
   c. Either a or b may be true, but one cannot tell without a placebo group.

3. The following statement about crossover designs are true:
   a. Statisticians fault the two-treatment, two-period crossover design (A-B or B-A)
   b. These designs may have a higher dropout rate than parallel group studies.
   c. They are attractive in conditions where there are large interindividual variations in response to drugs or in disease mechanisms.
   d. All of the above

4. Considering clinical trials in your area of interest:
What problems are posed by heterogeneity of disease mechanism? What approaches are currently being taken to minimize the difficulties they cause in clinical trials?
What are the potential issues regarding assay sensitivity (if any) for key clinical outcomes?